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INTRODUCTION

LOUSE-BORNE relapsing fever is 'the least well known of the quarantinable diseases' (Gear and Deutschman, 1956). Little is understood of where it lurks between epidemics and of how it suddenly springs up after silent intervals of several years. At present, the only definite endemic focus of louse-borne relapsing fever in the whole world is in Ethiopia (Sparrow, 1962), which reports several thousand cases annually to the World Health Organisation, the figures for 1966 and 1967 being 4210 and 4884 (*World Health Statistics Report*, 1968). It is possible that there are still small foci in the Balkans, the Peruvian Andes and in China (Gelman, 1961); there has been no information out of China for over 20 years. It is the 'most epidemic of the epidemic diseases' and its 'potential danger . . . remains the same as that at the time of the first pandemic of this century, which caused more than 50 million cases and certainly more than five million deaths. This was proved by the evolution of the second pandemic in which, despite the use of potent insecticides for louse control and penicillin for the treatment of the sick and of the comparatively short duration of the pandemic (less than five years), the number of cases was . . . not under 10 million' (Baltazard, 1962). 'From the epidemiological point of view the existence in Ethiopia . . . of a vast focus of louse-borne relapsing fever poses an important problem in prophylaxis in the country itself and on the international scale' (Sparrow, 1962).

The presence of this endemic focus presented the unusual opportunity to study relapsing fever in detail, an opportunity denied in the chaos of an epidemic. Our interest in the subject was first aroused in 1965 by the unexpected death of two patients who, having recovered from the crisis which follows treatment, appeared to be well but died quietly in the night. In 1966 we observed the haemodynamic changes which characterized this reaction (Parry, Bryceson, and Leithead, 1967) and the next year we looked more closely at the febrile and pressor phase of the crisis and the white-cell changes that accompanied it, postulating the release of endogenous pyrogen as its cause (Schofield, Talbot, Bryceson, and Parry, 1968). In 1968 we continued our study of the crisis with special reference to the cardio-respiratory and haematological changes and to the role of pyrogen. We present here the results of these investigations together with detailed results of our clinical and laboratory studies of the disease and attempt, by combining our findings with those of numerous others workers, to describe what happens in this disease, and to discuss the ways in which it kills.

THE EPIDEMIC HISTORY OF THE DISEASE

Hippocrates (translated by Chadwick and Mann, 1950), tells how, after a particularly bad winter and spring, a series of fevers hit Thasos. One of these, the 'causus' or 'ardent fever', can be clearly identified as relapsing fever from his clnical and epidemiological description.

It seems likely that the Yellow Plague which ravaged Europe in about A.D. 550 was relapsing fever (MacArthur, 1959); but the five epidemics known as the English Sweat which occurred between 1485 and 1551 (Caius, 1552; Gerster, 1916; Shaw, 1933) probably included cases of 'influenza' and typhus as well as of relapsing fever (Greenwood, 1935; Martini, 1955). The Famine Fevers of the seventeenth and eighteenth centuries included the Spotted Fever, or typhus and the Yellow Fever, or relapsing fever (MacArthur, 1957). Rutty (1770) in Dublin was the first to distinguish the two diseases. In England in 1727–29 an outbreak wiped out whole villages in Gloucestershire. Ireland, always a focus, suffered severely in 1739. In Scotland in 1841 an epidemic began in Fife and spread south to Edinburgh, Glasgow, and thence to England and the American Colonies. It was in this epidemic that Craigie (1843) in Edinburgh first used the name relapsing fever and Henderson (1844) compared the post-mortem appearances with those of typhus, which was also epidemic then. Twenty years later another English outbreak swept across Europe, after which little was heard of the disease until the First World War (Martini, 1955). The Greek army all got it in the Balkans. In Serbia, in a population of three million, there were half a million cases and over 10 0000 deaths. After the First World War the disease really got going and, largely through the agency of the Office International d'Hygiene Publique which had been set up in 1907, figures became available that showed for the first time its terrible power. Statistics collected after war from refugees fleeing famine and facing sickness are inevitably approximate, incomplete, and sometimes contradictory, but it is generally agreed that they are gross underestimates. The figures for the major epidemics of this century are given in Table I. There were extensions of these epidemics, notably into Turkey and Persia in 1920–1 (Willcox, 1920) and again into the Middle East after the Second World War (e.g. Haddad, Sheiban, and Budeir, 1946). There was an outbreak in Korea after the war there (Anderson and Zimmerman, 1955). This last outbreak suggests that a Chinese focus still persists. It is, however, with the African epidemics that we are concerned.

Louse-borne relapsing fever is old in Africa. El Ramly (1946) quotes a thirteenth-century description of the disease in Egypt and states that Napoleon's army suffered from it; Kamal, Anwar, Messih, and Kolta (1947) say there was an outbreak there in 1884. In 1910 Sergent and Foley in Tunisia, and in 1912 Nicolle, Blaizot, and Conseil in Algeria, reported the epidemic spread of louse-borne relapsing fever, the first case of which had been noticed in the Fezzan in 1903. By 1915 the disease had reached Egypt where 3 9722 cases were reported in four years (Stuart, 1945), and in 1919 it met up with the epidemic which had pursued the armies and the refugees through the Middle East (Willcox, 1920). With the end of hostilities soldiers and workers were repatriated from the Middle East. One of these introduced the disease into Guinea, and started an epidemic in May 1921 which literally decimated the population of the Sudan belt of tropical Africa, being arrested only 'by the nakedness of certain forest peoples' (Mathis, 1931). Kerrest, Gambier, and Bouron (1922) recount beautifully the origin and early spread of the epidemic, while Le Gac

TABLE I

The Major Epidemics of Louse-borne Relapsing Fever this Century

	Date	*Place*	*Origin of infection*	*Spread*	*Number of cases*	*Population morbidity*	*Number of deaths*	*Population mortality*	*Case mortality*
1.	1910–15	N. Africa[1]	Fezzan Desert	N. Africa	?				
2.	1915–19	Egypt[2]	N. Africa		39 722				
3.	1919–23	E. Europe	Indiginous	Russia C. Europe	13 000 000		5 000 000[4]		
4.	1921–30	W. Africa	Soldier from Levant[5]	Guinea Niger Chad (1925–1928) Sudan Senegal Gold Coast Nigeria (Kano) U. Volta	9803[7]	3·4%[7]	100 000[3] 5832[7]	37–40%[3] Darfur 21%	51–73%[7]
				TOTAL	128 750[9] ?	10%[8]	20 000[8] ?	10%[8] 5–25%[8]	57·7%[9] 0·6–46·5%[10]
5.	1936	Sudan	'Westerners' returning from Abyssinia[11]	All Sudan					
6.	1943–45	N. Africa	Italian P.O.W.[10] (Algeria) Fezzan Desert[12] (Tunisia)	Fezzan Algeria Tunisia Morocco	400 000[3] 400 000[3] 180 000[3] 1 000 000	50%[3] 5% troops[13] 10%[13]	1500[3] 50 000[3]		10%[3] 5–6%[12] 10–12%[12] 2–3%[12] 10%
7.	1945–7	Egypt[14]	N. Africa		1 287 760[3]	8%			3%

[1] Nicolle and Blanc (1914). [2] Stuart (1945). [3] Sparrow (1958). [4] Sparrow (1962). [5] Kerrest *et al.* (1922). [6] Mathis (1931).
[7] Le Gac (1931). [8] Hindle (1935). [9] McCulloch (1925). [10] Greaves *et al.* (1945). [11] Kirk (1939). [12] Stuart (1945).
[13] Mooser (1958). [14] El Ramly (1946).

(1931) describes the fury with which it hit Chad where the case mortality reached, in one area, 73 per cent. In Kano alone 12 8750 people died of the disease, and in Darfur 20 per cent of the population succumbed. The final toll of this epidemic will never be known.

The disease next appeared in the Sudan. Kirk, in 1939, described how 'Westerners' (the wandering inhabitants of north-western Sudan) returning home from Abyssinia, ill contented with the conditions they found under the Italian occupation, straggled off the highlands by many routes bringing the spirochaete with them and spreading relapsing fever diffusely through the Sudan. At the same time and for the same reason there was an outbreak in Kenya (Garnham, Davies, Heisch, and Timms, 1947). In 1942 louse-borne relapsing fever reappeared in the Fezzan area of southern Libya. In a few months the disease spread fast through Tunisia, Algeria, and Morocco. Once again there are official figures (Stuart, 1945; Greaves, Gezon, and Alston, 1945) and unofficial estimates (Mooser, 1958; Sparrow, 1958) of the morbidity. The latter are more likely to be correct for at the time of the outbreak Greaves, Gezon, and Alston (1945) in Tunisia and Grenoilleau (1946) in Algeria considered that the official figures represented only one-fifth or one-tenth of the true incidence. It seems likely that there were about one million cases with 5 0000 deaths. Ten per cent of the population suffered in Tunisia, and 5 per cent of the troops in Algeria. The case mortality varied from less than 1 per cent of the soldiers who received treatment to 9 per cent of the paupers who did not. Egypt once again received the aftermath of this epidemic with an estimated 128 7760 cases (Sparrow, 1958) which is 10 times the official figure (Kamal, Anwar, Messih, and Kolta, 1947) and 8 per cent of the population. In some country areas 45 per cent of the population were afflicted, while in one hospital alone El Ramly (1946) treated 2682 cases in six months. The epidemic was finally brought under control by mass treatment with arsenic and DDT, after 3 0000 had died. Fingers of relapsing fever reached out into the Mediterranean and Middle East in 1945 (e.g. Haddad, Sheiban, and Budeir, 1946; Gelman, 1961) but failed to take hold and the epidemic died out in 1946. There was an interesting extension into Kenya in 1945 (Garnham, Davies, Heisch, and Timms, 1947) when an Arab dhow bringing cloth merchants from Arabia imported the disease and started a brisk epidemic of 2000 cases with a mortality of 40 per cent in the untreated.

No further epidemics of louse-borne relapsing fever have been seen since 1946. Under what circumstances may the disease reappear and from what reservoir?

THE ENDEMIC FOCUS

In the days when we all had lice it was easy for the organism to persist, and any movement of people, however small, ensured the spread of relapsing fever. Now fewer people have lice, but no country of the world is without them. For the transmission of any insect-borne disease the organism, the vector, and the susceptible host must coincide, which they do in Ethiopia.

Although they are near the equator, the Ethiopian highlands can be quite cold, particularly during the long rains from June to September which are locally regarded as the winter months; in the dry weather water is scarce. Few people are able to wash themselves or their clothes regularly, and so the lice multiply. The susceptible population in Ethiopia is mainly the migrants, either seasonal labourers or unemployed who provide the new hosts which the organism needs to keep the disease smouldering. From time to time isolated flare-ups of relapsing fever, not of epidemic nature, but enough to involve a few hundred people are common (Wolman and Wolman, 1945; Rÿkels, 1968). A comparable situation existed along the Yangste river in China in the 1930s (Robertson, 1932). Typhus and smallpox are also endemic in Ethiopia for the same reasons. Helène Sparrow (1958) examined the situation in Ethiopia in 1955 and was able to demonstrate an enormous reservoir of louse-borne relapsing fever. She expressed the fear that 'conditions in certain parts of the African continent . . . constitute . . . a situation favourable to a recrudescence of relapsing fever'.

The ecology of relapsing fever in Ethiopia seems ideal for the maintenance of the disease. Many workers (see Felsenfeld, 1965) have felt that the mysterious reappearances of the disease indicated either an animal reservoir or a transformation of the tick-borne spirochaete, which is ubiquitous in Africa, into the louse-borne (Nicolle and Anderson, 1927; Boiron, 1948). No naturally occurring animal infection of *Borrelia recurrentis* has ever been found, though many of the tick-borne strains have animal reservoirs (see Felsenfeld, 1965).

As a reservoir the louse is a dead end. It has to feed on blood daily, lives only a few weeks, and does not transmit the spirochaete transovarially. It has often been observed that the louse could transmit the tick spirochaete (e.g. Boiron, 1948; Heisch, 1950) though the reverse is not true (Kirk, 1938; Heisch, 1950), and this led to several attempts to transform, by repeated passage, the characteristics of the tick-borne spirochaete into those of the louse-borne spirochaete. Apart from one partial success by Sparrow (1962), all attempts have failed. Balthazard, Mofidi, and Bahmanyar (1947) tried to bring about reversion of the louse-borne spirochaete to the 'primitive' tick-borne form, but the results of their experiments were contradictory. Attempts to find naturally occurring spirochaetes with properties intermediate between the two have also failed with the possible exception of one of Sparrow's isolates in Tunis in 1950. Cunningham, Theodore, and Fraser (1934) discovered two human relapse strains (strains H and I) which were scantier, longer living, and slower to multiply than the original strain, and wondered if this might represent a resting stage of the organism in humans. At the end of the Darfur epidemic Atkey (1931) described subacute or ambulatory cases which were impossible to detect clinically. Man remains the sole reservoir of louse-borne relapsing fever, and an endemic focus, as is present in Ethiopia, is capable of starting a widespread epidemic. It is interesting that the African epidemics have had 20-year cycles, 1903, 1923, 1943. This may be simply the result of political and military events; but 20 years is the time it takes for a non-immune generation to grow up.

Let us then re-examine two of the earlier African epidemics, namely those which arose out of the Fezzan desert in 1903, and 1943. It seems to us unlikely that the sparse population of the Sahara Desert, albeit nomadic, could act as an endemic focus for a disease so dependent upon people for its survival. In the 1880s the Mahdists were beseiging the Christians of the Ethiopian plateau (Doresse, 1959) and in 1887 they climbed up and sacked Gondar. The next year the Emperor Yohannes replied by descending and killing 6 0000 Mahdists at Matamma. Skirmishes continued for the next few years. In 1898 the Mahdists were defeated by Kitchener, but there was not a great diaspora. Most returned to their villages, some to Darfur and a few perhaps to Chad. A more important movement of people, however, took place a few years earlier, in 1883–5, when Rabih Zubair and his followers moved west, settling at Bagirim near Lake Chad in 1894. Lake Chad is not only on the great East–West pilgrimage route from Senegal to Arabia, but is also the start of the trade route through the Fezzan to Libya, Algeria, and Tunisia. In 1900 Rabih Zubair was defeated and his people dispersed (Sanderson, 1969). It is not difficult to imagine, but impossible to prove, that one of these movements took relapsing fever from Ethiopia to the Fezzan.

It is generally assumed (Stuart, 1945) that in 1943 the disease once again arose out of the Fezzan desert, where Gras (quoted by Gaud and Morgan 1947–8) traced the outbreak to the Megarha nomads. Sparrow (1958) points out that troops occupied Fezzan at the end of 1942, four months before the first case was reported, and Greaves, Gezon, and Alston, (1945), who have examined the start of the epidemic minutely, state that the first patient in Tunisia was an Italian prisoner of war recently arrived from Tripolitania. Italy had finally surrendered in Ethiopia in November 1941. There were, however, no cases among Italian prisoners of war held in Sudan (Carew, 1957) nor among repatriated civilians, but once again there were refugees travelling the old trade routes. We, like Sparrow (1962), consider that the origin of the 1943 epidemic could possibly have been in Ethiopia.

Even if these suppositions are incorrect, the danger of the Ethiopian focus in any time of 'overcrowding, filth, famine or distress' when 'lice follow the army' (Willcox, 1920) will become apparent, and now 20 years later a fresh non-immune population has grown up throughout Africa. There is, at the time of writing, two-way refugee traffic on the Sudan–Ethiopian border and cases of louse-borne relapsing fever have been found near Khartoum (Abdalla, 1969). The danger of a new epidemic is great.

THE HISTORY OF LOUSE-BORNE RELAPSING FEVER IN ETHIOPIA

The Emperor Menelik II founded Addis Ababa in 1895. In 1910 his physician Mérab (1912) wrote that he had heard of cases of relapsing fever, but had not himself seen any in the capital. It is not clear whether he was referring to the louse or the tick-borne variety. Brumpt (1901) had dismissed the association of

tick-bites with fever, but after the recognition of tick transmission by workers in East Africa he demonstrated the spirochaete in the blood of monkeys which had been bitten by ticks sent to him from Harar and Dire-Dawa (1908). Doreau saw spirochaetes in the blood of an askari in the Danekil in 1908, but Costa (1928) was the first to see what was probably the louse-borne spirochaete during an epidemic in Adua and Axum in 1918. The disease is clearly very old in Ethiopia; Napier's expedition exported it to India in 1868 (*Lancet*, 1869).

In the 1920s Nägelsbach (1934), who had already found the disease in Gore in the south-western highlands, and Bergsma (1928, 1929), both found cases in Addis Ababa. Nägelsbach said it was a common disease and frequently fatal; there might be up to 10 or 20 cases in any one compound in the city. He noticed that lice were numerous and ticks absent, and that arsenic cured the disease if it was given early, but that later on in the attack it was unable to prevent death. Bruns (1937) also noticed how common the disease was in the highlands and said it was endemic in all the stations along the railway line from the Red Sea coast to the highlands. He distinguished the louse-borne disease of the highlands from the tick-borne disease of the south-eastern lowlands and described an epidemic of louse-borne relapsing fever at Jigjiga in 1929, where the Somalis, weakened by smallpox and famine died by the thousand—he counted 1200 fresh graves most of which contained more than one corpse, and reckoned that the mortality varied from 5 per cent to 10 per cent depending on who got the disease. He also described the clinical features of the illness.

In their 50 years in Eritrea and five years in Abyssinia, the Italians did a lot of medical work. Bucco (1965) has reviewed most admirably 109 papers written by them on relapsing fever in Ethiopia. The disease plagued their troops, 599 of whom suffered from it in the first year of the Abyssinian occupation, and was ranked among the four biggest menaces along with malaria, meningitis, and typhoid. In 1930 De Paoli and later numerous other workers (e.g. Sibilia, 1937) demonstrated that the disease was louse-borne. Outbreaks were described all over the highlands, in Axum, Macale, Debra Berhan, Lasta, Fiche, Gondar, the Simien Mountains, and Addis Ababa where the disease remained endemic. Bucco (1965) records fully their clinical and pathological observations. The over-all mortality of the disease was 33 per cent of the untreated and 4 per cent of the treated.

During the 1941 Ethiopian campaign it was the British turn to encounter the disease. Cases first appeared among the Gold Coast troops in June 1941 (Charters, 1942; Minett, 1942) and there were nine deaths in the first 28 cases, although the official figure is no deaths in a total of 78 cases (Carew, 1957); Minett thought that the high altitude rendered these men especially susceptible. Robinson (1942) described the clinical picture of the disease, and found the mortality in the treated to be 3·5 per cent (see Table III). Wolman and Wolman (1945) conducted some elegant experiements with spirochaetes in lice and in culture (*vide infra*: The Organism).

Since then only Helène Sparrow (1958) has shown any interest in relapsing fever in Ethiopia. We believe that there are not less than 1000 cases of louse-borne relapsing fever in Addis Ababa each year, and that the mortality is about 5 per cent. It is mainly the destitute migrants who get the disease. The annual number of cases in the whole country could exceed 1 0000.

THE ORGANISM AND ITS VECTOR

The taxonomy of the genus *B. spirochaetes*, which cause relapsing fever, has been a matter of confusion and debate since 1873, when Obermeier described the spirochaete he had seen in the blood of a patient five years earlier. Johnstone (1942) has discussed the taxonomic problems. Most authorities accept the nomenclature given by Felsenfeld (1965) whose review of the literature is exhaustive; in this the louse-borne spirochaete is known as *B. recurrentis* and the tick-borne spirochaetes are named according to their tick vector.

Mackie, in India in 1907, was the first to find the spirochaete in the louse, and Sergent, Gillot, and Foley (1911) and Nicolle, Blaizot, and Conseil (1912) separately described its mode of transmission. After feeding on infected blood, the spirochaete passes from the gut into the coelomic cavity of the louse. During this passage the spirochaete may (Robertson, 1932) or may not (Nicolle, Blaizot, and Conseil, 1912) be detected in the louse. Sparrow (1958) has shown that this so-called 'negative phase' is an artefact due to faulty technique and Heisch and Harvey (1962) have described in detail the course of the organism within the louse. Pillot, Duponey, and Ryter (1964) have shown that granular forms are degenerate. Since the coelomic cavity in the louse does not communicate with the gut or mouth, only the crushed louse is infective. The louse remains infective all its life, which is a few weeks. Periodicity in the louse has never been observed. The periodicity of *Borrelia* in its host—the relapse phenomenon—has excited many since the earliest days.

Meleney (1928) using splenectomised squirrels identified six relapse strains which were distinguishable by agglutination with specific immune sera. Russell (1931) demonstrated the capacity of *B. recurrentis* to produce several serological variants in one host, each variant being equally pathogenic. Those experimenters (Meleney, 1928; Cunningham, Theodore, and Fraser, 1934; Russell, 1932; Adler and Ashbel, 1937; Coffey and Eveland, 1967; Balthazard, Seydian, Mofidi, and Bahmanyar, 1949) who have used sensitive techniques (see Schuhardt, 1942; Felsenfeld, 1965) have found that each antigenic variant, strain, or type retains its identity on passage for at least one year but loses it on relapse and is unable to reinfect the same animal. Such specific variation, which has been observed also in human epidemics (Toyota, 1919) probably accounts for reinfection after spontaneous cure. Coffey and Eveland (1967) showed that relapse strains follow a constant order and attribute this phenomenon to an inherent property of the spirochaete rather than to a specific immune response on the part of the host (see also Wolman and Wolman, 1945). Other workers consider that the host's immune response plays the major role in bringing each

attack to its end; infection with a single spirochaete of *B. turicatae* in rats produced a relapsing infection (Schuhardt and Wilkerson, 1951) and as relapse strains do not lose their identity on passage it seems likely that the immune response is important. Like Felsenfeld (1965), we think that periodicity and relapse constitute an example of host-parasite adaptation which results in a 'cyclical disease due to a cyclical agent'.

The disappearance of the spirochaete from the blood in each remission is not absolute; Robinson (1942) found that 38 per cent of blood slides taken from patients in the afebrile period were positive, but this figure is higher than most. The ability of *Borrelia*, especially the tick-borne strains, to persist in the brain and in the eye during remission after treatment with arsenic or with penicillin, or even after apparent cure is well known (e.g. Hindle, 1935; Schuhardt and Hemphill, 1946; Schuhardt, 1952; Pages, 1952). The virulence of the spirochaete probably waxes during an epidemic due to repeated passage (Wolman and Wolman, 1945) and starts to wane again as the epidemic dies out (Kirk, 1939). The infectivity of the spirochaete varies with the season of the year (Balthazard, Seydian, Mofidi, and Bahmanyar, 1949; Sparrow, 1958). Pillot and Ryter (1965) describe the electron microscopic appearance of *Borrelia* as being close to that of *Eubacteria*.

THE HOST

Man is the only host of louse-borne relapsing fever. With the possible exceptions already mentioned (Atkey, 1931; Cunningham, Theodore, and Fraser, 1934) no chronic infections have been recorded and immunity is thought to be sterile (Russell, 1936). All people who have not had the disease before are susceptible (El Ramly, 1946) though there are occasional individuals who for unknown reasons may fail to contract it (Sparrow, 1955) when artificially inoculated. Mental patients treated by 'recurrento-therapie' with *B. recurrentis* developed a normal infection, which terminated spontaneously without any ill effects (Sparrow, 1955); many of them are said to have benefited from the experience. It has been observed in most outbreaks that it is the poor and overcrowded, malnourished and diseased who are especially susceptible. This is probably due more to the enhanced breeding of lice than to increased susceptibility, though there is experimental evidence that protein deficiency diminishes the host's resistance to *Borrelia* (Guggenheim, Buechler-Czaczkes, and Halevy, 1951). Our Ethiopian patients are good examples of the sort of people who are liable both to catch and spread the disease and so it is appropriate to describe them here.

PATIENTS STUDIED

Between July 1966 and August 1968 we studied 62 patients at the Princess Tsehai Memorial Hospital and St. Paul's Hospital, Addis Ababa. The background of these patients is shown in Table II.

Fifty-five patients were aged between 10 and 29 and males outnumbered

TABLE II

Background Information about the 62 Patients Studied

Age		*Sex*		*Tribe*		*Religion*		*Occupation*		*State*		*Origin*		*Address*	
10–19	27	Male	46	Amhara	13	Christian	26	Coolie	18	Middle Class	4	Immigrant	34	Addis Ababa 'Mercato'	24
20–9	28	Female	16	Galla	9	Moslem	4	Farmer	4	Poor	10	Local/ unknown	28	Addis Ababa other	11
30–9	4			Gurage	7	Unknown	32	Housewife	4	Very poor/ destitute	22			Countryside	5
40–9	3			Others/unknown	33			Merchant	2	Unknown	26			Unknown	22
Mean	22							Student	2						
								Jobless	3						
								Others/unknown	29						

females 3:1. The Christian majority reflects the dominant religion of the local countryside and not of the 'mercato' or market where the majority are Moslems in established business. Thirty-four of our patients were recent immigrants into Addis Ababa (five days–10 years, mean four years) who had come in search of work and either had failed to find it or were earning a precarious living as coolies. Many were homeless and most of them lived in the poor area around the 'mercato' on balconies or in little shelters where they huddled together at night. Under these conditions lice thrive; as new immigrants arrive the lice move over and the spirochaete finds fresh, non-immune blood. Forty-four of our patients came from St. Paul's Hospital, which is a free hospital, while only 18 patients presented themselves at Princess Tsehai Memorial Hospital, which is a paying hospital. This emphasizes the social class affected. In all cases the diagnosis was confirmed by the finding of spirochaetes in a stained peripheral blood film, and the patient was treated within a few hours of admission.

In a pandemic all ages are affected and the M:F ratio is 1:1 (El Ramly, 1946) but in a more localized peacetime outbreak, or endemic situation young males are disproportionately affected. Robertson (1932) found in Shanghai that most of his patients were coolies between the ages of 20 and 40. Eighty per cent of Chung and Chang's (1939) patients in Peking were between the ages of 10 and 39 and the M:F ratio was 5·9:1. The pattern of migration has also been noticed by Rÿkels (1968) in Kaffa Province, south-western Ethiopia. The majority of his patients were seasonal coffee pickers, who were poor young men separated from their families, crowded together in unhygienic conditions. His peak incidence was determined partly by the coffee seasons while ours was determined wholly by the cold rainy season. Wandering, for work or from war, has determined the age and sex distribution of many outbreaks.

THE DISEASE

Clinical Picture

Symptoms

The symptoms of our patients are summarized in Table III.

All patients had many symptoms, none of which was particularly characteristic. Nevertheless the disease had a pattern. The onset was sudden with chills, fever, and slight malaise. During the first two or three days there were frequent chills and the patients became aware of increasing fever which did not abate, accompanied by headache and progressive malaise and weakness. In some cases the headache was severe and frontal. An early symptom in many cases was severe dizziness which was difficult to define but did not seem to be true vertigo. Some had nightmares. A bitter taste, thirst, and dysphagia were associated with anorexia, and later nausea and vomiting in a few cases. Generalized aches and pains were common after the first few days. These were often localized in the muscles and joints, especially the knees, elbows, and lower back; they were not as severe as in dengue, but were severe enough to be volunteered by the patients.

Still later in onset were abdominal pains which were mentioned by two-thirds of the patients. The pain was felt mainly in the epigastrium or hypochrondrium and was associated with the rapidly enlarging liver and spleen. This made breathing painful and may have been the cause of the high incidence of chest pain in this series, a symptom elicited by questioning. Left shoulder pain in two of the patients was probably caused by perisplenitis.

TABLE III

Symptoms of 62 Patients with Louse-borne Relapsing Fever

	%		%
Fever	97	Chest pain	65
Chills	90	Arthralgia	65
Headache	87	Cough	53
Backache	84	Dysphagia	48
Anorexia	78	Muscle tenderness	44
Muscle pain	78	Vomiting	34
Dizziness	74	Epistaxis	23
Sweating	74	Dark urine	23
Abdominal pain	68	Dyspnoea	18
Nausea	65		

Coughing was another symptom at this time although in some cases it began earlier. It was painful and irritating and sometimes productive of mucoid frothy sputum.

Epistaxis was seen in one-quarter of our cases. Early in the illness it was usually mild but, later, four patients bled alarmingly. Two jaundiced patients had severe epistaxis even after spirochaetes had disappeared from the blood. Dark or red urine was noticed commonly, usually by deeply jaundiced patients.

The patients came to hospital 3–11 (mean 5) days after the first symptom.

Signs

The patients with relapsing fever often presents a recognizable picture. He lies on the ground or sits silent and uncomplaining, his expression glazed, his manner apathetic, and his mind dull or confused. The forehead is hot and dry but the hands are cold. He may be shivering or breathless. Epistaxis, purpura, jaundice, or tenderness over the liver or spleen make one sure of the diagnosis.

The signs which we were able to elicit in the 62 patients are summarized in Table IV. The number and intensity of the signs varied greatly from patient to patient.

Purpura varied from a petechial rash in the early stages to extensive ecchymoses later. This rash was commonest over the flanks and shoulders. The conjunctival vessels were congested and conjunctival haemorrhages were occasionally seen, making the diagnosis of iritis difficult and masking the presence of jaundice which was present in one-third of the patients. One patient had haemorrhages and exudates in the retinae for which no other cause could be found.

All patients had a tachycardia which was typical of any febrile state. Four patients had ectopic beats. Gallop rhythm was heard in a quarter of the patients; it was usually caused by an atrial sound. The ejection systolic murmurs, and often an accompanying loud pulmonary second sound, were doubtless the result of increased blood flow.

TABLE IV

Physical Signs in 62 Patients with Louse-borne Relapsing Fever

	Percentage of cases	
General		
Fever (temperature over 38 °C)	94	range 36·1–41·0, mean 39·1
Purpura	17	
Jaundice	34	
Cardiovascular		
Tachycardia (pulse-rate over 90/min)	100	range 90–164, mean 102
Ectopic beats	6	
Hypotension (systolic pressure under 90 mmHg)	12	range 64–130, mean 120
Gallop rhythm	24	
Systolic murmur	14	
Respiratory		
Tachypnoea (respiratory rate over 20/min)	100	range 20–72, mean 36
Added sounds	3	
Abdominal		
Liver tender	63	
palpable	47	
Spleen tender	55	
palpable	34	
Neurological		
Confusion	45	
Dysphasia, delirium, coma (1 case each)	4	
Meningism	39	
Ptosis (2 cases)	3	
Iritis (2 cases)	3	
Retinae: congested veins, haemorrhage and exudate (1 case)	1	
Tender muscles	44	

Tachypnoea was extremely common. One patient had a respiratory rate of 75 per minute and was found to have radiological evidence of pulmonary oedema. In the majority of patients no added sounds were heard in the chest despite the frequent cough.

Tenderness over the liver and spleen was usual, though the organs themselves were less often palpable. They could descend to four or five fingers' breadth below the costal margin in a few days. In two patients the spleen became especially tender and in one of them it continued to increase in size; it is likely that they had had splenic infarcts.

TABLE V

Symptoms Reported in Epidemics of Louse-borne Relapsing Fever

No.	Author	Country	Patients	Sex ratio M:F	Age	Occupation	Status	Length in days: Attack	Length in days: Remission	Number relapses (% relapsed)	Fever	Chills	Headache	Dizziness	Confusion	Sweating	Anorexia	Nausea	Vomit	Abdominal pain	Throat	Dyspnoea	Chest pain	Cough	Muscle pain	Joints	Backache	Epistaxis	Dark urine	Other symptoms
1.	Willcox, 1920	Persia	241				Soldiers	5–7					5%		29%				9%											Nightmares, mania
2.	Beveridge, 1928	Sudan	160	1:1	3–70 yrs.					1			+						31%							+		+		Diarrhoea 47%, weakness in most; insane 1
3.	Robertson, 1932	China	371	19:1	All ages, Maj. 20–40	Coolies, beggars	Poor	7	8	22%	100%	100%				100%	100%	100%	100%	50–70%					75%	Occasional 'arthritis'		+	Occ.	Diarrhoea rare. Constipation frequent
4.	Chung and Chang, 1939	China	337	17:1	All ages	Soldiers beggars, coolies, vagabonds	Poor	7	7·1	1–5	96·8%	72·7%	76·2%		0·6%	27·3%	69·2%	29·7%	29·1%	19·0%	53·9%		48%	41·2%	58·8%	Occasional		27·3%		Constipation 47·4%. Ear disturbance 4%. Relapses after treatment 5·6%
5.	Charters, 1942	Ethiopia	32					2–5														30%		+ (spirochaetes +)						Diarrhoea 6·3%. Deafness 3·1%
6.	Robinson, 1942	Ethiopia	340				(m.)			(16%)														+	Occasionally tender			12%		
7.	Greaves *et al.*, 1945	Tunisia	40		All ages					1–5	100%	27·5%	90%						47·5%	10%					60%			17·5%		Weakness 16%
8.	El Ramly, 1946	Egypt	2682	1:1	All, 20 peak		Destitute poor	7	6	(67%)	+	+	+			+		+	+					+	+			3%		
9.	Haddad *et al.*, 1946	Cyprus	200			Workers		6			90%	90%				After crisis			49%									24%		
10.	Wolff, 1946	Assam	134			Chinese soldiers	Poor mal-nourished	7–12			88·8%	47·8%		28·3%								Common		64·4%	86·6% tender			4·6%	+	Weakness 40·3%. Diarrhoea 30%. Constipation 39·8%
11.	Garnham *et al.*, 1947	Kenya	430				Poor		2–7	(32%)	+	+	+						+	33%			+ 'Fibrositis'	34%	63%	63%	+ Severe			Diarrhoea 28%. Temp. fell by crisis 67% lysis 33%
12.	Rȳkels, 1968	Ethiopia	67	21:1	15–30 + 1 child 6 mths.	Coffee pickers				2 (3%)	+	+	+		35% 9% dis-oriented				28%	40%				46%	68%	43%		17%		
	This series	Ethiopia	62	3:1	10–50, mean 22	Immigrant coolies	V. poor				97%	90%	87%	74%	45%	74% mild	78%	65%	34%	68%	48%	18%	65%	53%	78% tender 44%	65%	84%	23%	23%	

Table VI

Physical Findings in Epidemics of Louse-borne Relapsing Fever

No.	*Author*	*Country*	*Temperature*	*Pulse*	*R.R.*	*B.P.*	*Conjuncti-vitis*	*Iritis*	*Tongue*	*Ronchi or rales*	*Cardiac murmur*	*Liver*		*Spleen*		*Jaundice*	*Meningism*	*Cranials I–XII*	*Other CNS*	*Rash pet./purp.*	*Bleeding (not epistaxis)*	*Other signs*	*Mortality*	*Causes of death*	*Complications*
												Large	*Tender*	*Large*	*Tender*										
1.	Willcox, 1920	Persia	103–104 °F									41%		70%		64%							9%		
2.	Beveridge, 1928	Sudan	38·8–41 °C	156/m max.					Furred moist	'Bronchitis'		44%	20%	52%	+	20%		VII, VIII 2 each					7%	Prolonged illness	Pneumonia 7%
3.	Robertson, 1932	China	104–105 °F			Normal				'Bronchitis' common		78·2%	+	<50%		4–70%			Delirium at crisis	2 cases			1·8%		
4.	Chung and Chang, 1939	China	38–40 °C				46·6%		*H. labialis* 32%	'Bronchitis' 14·8%		40·9%	±	69·2%	1·8%	29·4%	1·8%			34·7%	Splenic rupture		6·2%		Pneumonia 5%
5.	Charters, 1942	Ethiopia					2/32			12/32			All	59·4%	40·6%	5/32 deep			Delirium 1 Neuritis 4						
6.	Robinson, 1942	Ethiopia							68% 4 stages		38·0%			89%	44%	72%			Meningitis, 3 cases died	Purpura 5%	Cerebral 3 (2 paralyses)		3·5%		Typhus 10% Malaria 6%
7.	Greaves *et al.*, 1945	Tunisia										45%	+	62·5%		7·5%				Petichiae 60%			0·6%–46·5%		
8.	El Ramly, 1946	Egypt								'Bronchitis' 7%		77%	60%	84% Infarct	25% 2·5%	22%		VII 3 cases		70% not in relapse	1%	Pregnancy 93% aborted	3%		Pneumonia 2·4% Pericardit 3%
9.	Haddad *et al.*, 1946	Cyprus	40 °C	Rapid					*H. labialis* 2 cases	'Bronchitis'+		90%	+	90% Infarct	+ 0·3%	78%	30%		Meningitis 3%	2%			2%		
10.	Wolff, 1946	Assam	104 °F	Rapid			8·2%			Transient 52%		16·4%	+	27·4%	+	11%			Myelitis, crisis convulsions	5·2%	4·5%	Deafness 45%. Parotits 5·9%	12%		5% Malaria 3% typhus
11.	Garnham *et al.*, 1947	Kenya	103–104 °F 2–7 days					Non-reactive pupils		Rare	2·4%	66%	+	75%	+	28%	+		Delirium			Heart enlarged. Pregnancy—3 aborted	4%		
12.	Rÿkels, 1968	Ethiopia	In 81% >38 °C	In 75% >100/m	In 64% >30/m	79% <100 mmHg	17%	Not seen			+	20%	60%	33%	40%	9%	7%		Comatose 2 cases	4% neck shoulders		Photophobia 43%	3%	Myocardial	Anaemia 20% Malaria+typhus
	This series	Ethiopia	36·1–41 °C (39·1)	90–164 (102)	20–72 (36)	64–130 systolic		3%	22% furred	3%	14% Gallop —24%	47%	63%	34%	55%	16%	39%	Ptosis 2 cases	Aphasia, delirium coma, 1 each	17%		Congested retinal veins. 2 abortions/6 pregn.	5%	Haemorrhage 1 'Coma' 1 'Post-crisis' 1	In crisis

Confusion was the commonest neurological sign. Occasionally meningism was sufficiently severe to suggest bacterial meningitis. We saw transient ptosis twice. One patient was dysphasic, another delirious, and a third arrived in coma. Tender muscles, which made measurement of the blood-pressure by sphygmomanometer uncomfortable, were often found.

Six of our patients were pregnant, two aborted, one gave birth to a live premature infant, and three pregnancies were uninterrupted.

Discussion

Although we came to recognize a pattern of symptoms and signs a comparison with 12 other reports of the disease, which is given in Tables V and VI, shows that there are differences between individual outbreaks. It is clear, however, that the systems hardest hit are the hepatic, renal, cardiovascular, respiratory, and cerebral.

It is agreed that after an incubation period of a few days, depending to some extent upon the infecting dose (Balthazard, Seydian, Mofidi, and Bahmanyar, 1949), the illness starts suddenly with chills and a rapidly rising fever which may not at first be apparent to the patient. The temperature soon reaches 39 or 40 °C and stays there in the majority of cases, not varying more than 1 or 2 °C throughout the 24 hours. Sweating is usually absent or slight and nocturnal and is not usually mentioned spontaneously by the patient. Headache has always been described as an early symptom. In our experience a cerebral symptom is usual at the onset; often this is simple dizziness. Willcox's (1920) troops suffered from 'terrible and barbaric' nightmares, as did Heisch (1950) himself when he was infected with *B. duttoni* and so also did one of us who became infected when blood from a patient spilt on his hands. Heisch also describes photophobia, a rushing in the ears, disorientation, and a transient aphasia. Thirst is instant and demanding.

Some workers found diarrhoea (Kerrest, Gambier, and Bouron, 1922) and constipation (Haddad, Sheiban, and Budeir, 1946) to be common but these symptoms probable mean typhoid or dysentry (Anderson and Zimmerman, 1955). Cough is common, and the sputum contains spirochaetes (Charters, 1942). In some series it is called bronchitis and labelled as a complication of the disease. Tachypnoea is a remarkable and constant feature and there may be actual dyspnoea (Charters, 1942). Epistaxis is common and early. Beveridge (1928) thinks it is commoner at a higher altitude, but our figures do not support this. We have confirmed Robertson's (1932) observation that epistaxis can start after the crisis.

Bleeding has often been reported in louse-borne relapsing fever. Early in the first attack petechiae develop in the skin and in all serosal membranes (El Ramly, 1946). Epistaxis is at first usually slight and transient (Robinson, 1942). El Ramly (1946, 1946*a*) pointed out that the petechial rash was not an indication of serious bleeding and did not affect the prognosis. He also repeated Craigie's (1843) observation that this rash never appeared in any of the relapses.

Later in the first attack serious bleeding may develop with severe and prolonged epistaxis (Robertson, 1932; Wolff, 1946). Haemorrhage may be meningeal (Babes, 1916; Willcox, 1920) subdural and cerebral (Anderson and Zimmerman, 1955; Bucco, 1965), gastrointestinal (Russell, 1931; Robinson, 1942) urinary (Wolff, 1946; Bucco, 1965), and serosal (Russell, 1931).

Abortion or miscarriage is the usual fate of pregnancy. That we had one live premature birth and three uninterrupted pregnancies is probably due to a standard of care not normally available in an epidemic. That congenital infection and abortion are the rule is clear from El Ramly's post-mortem studies (1946, 1946*a*). Jaundice has been a variable sign: from 7 per cent (Greaves, Gezon, and Alston, 1945) to over 70 per cent (Robinson, 1942; Haddad, Sheiban, and Budeir, 1946). This may imply different degrees of liver damage, but the observation is so subjective and jaundice develops so quickly that such variation is to be expected. All are agreed, however, that hepatomegaly and splenomegaly are common. Exquisite abdominal tenderness and rigidity such as we elicited in one patient who later died in shock following intraperitoneal haemorrhage, can be caused either by a generalized serosal ooze or by rupture of the spleen (Haddad, Sheiban, and Budeir, 1946; El Ramly, 1946*a*; Legerton and Chambers, 1950).

Few cardiological abnormalities have been reported but Robinson (1942) was impressed by the frequency of cardiac murmurs. Kerrest, Gambier, and Bouron (1922) considered the heart 'immune'. Wolff (1946) noticed that on admission his patients were either hot and dry with a fast full pulse, or cold and clammy with a thin pulse; these latter patients had probably undergone a spontaneous crisis.

Many neurological signs are reported. None is characteristic but all are suggestive. The neck stiffness is seldom as severe as in bacterial meningitis unless there is a subarachnoid haemorrhage (e.g. Babes, 1916). Other signs include aphasia (Bruns, 1937), delirium (Chung and Chang, 1939; Charters, 1942), mania (Willcox, 1920), amaurosis, iritis and blindness (Mackenzie, 1854; Mooser, 1958), deafness and myelitis (Wolff, 1946). Coma can be due to 'meningitis', cerebral haemorrhage, hepatic failure or possibly renal failure. It can also occur in or after the crisis. Charters (1942) also noticed peripheral neuritis but this could possibly have been due to arsenic. Neurological signs are commoner in tick-borne relapsing fever (Scott, 1944).

Several writers have reported 'complications'. Some, such as cerebral haemorrhage, splenic infarction (El Ramly, 1946), and sterile splenic abscess (Nasr, 1948) are probably due to relapsing fever, while others such as lobar pneumonia (Chung and Chang, 1939) diarrhoea, endocarditis, pericarditis, empyema, and infected splenic infarcts are probably due to secondary bacterial infection (Kulescha and Titowa, 1923; Anderson and Zimmerman, 1955). The crisis is an integral part of the disease treated or untreated, and is not a complication.

Descriptions of the untreated course are given in all the earlier accounts. In Ethiopia Bucco (1965) described an incubation period of 4 to 14 days, a

febrile period of 4 to 10 days, a remission of 5 to 6 days and up to four relapses, reduced to two or three by treatment with arsenic. Each attack ends by crisis, which may be fatal (Nägelsbach, 1934). The crisis has been one of our main interests and is described in detail below. In the afebrile period malaise continues. As far as we could tell all our patients presented themselves during their first attack. Because treatment was available and tetracycline was used (*vide infra*: Treatment) we saw no relapses. The features of the relapse are those of the original attack, with the exception of the rash, but are of diminishing severity (El Ramly, 1946). Death in louse-borne relapsing fever, as opposed to tick-borne relapsing fever, is in the first attack. Purely cerebral relapses have been observed in tick-borne relapsing fever (Lodewyckx, 1938; Trowell, 1951). The clinical differences, such as they are, between louse-borne relapsing fever and tick-borne fever, have been listed by Coghill (1949) and Southern and Sanford (1969).

Benhamou (1945) who witnessed the epidemic in Morocco, divided the manifestations of louse-borne relapsing fever into six syndromes. We think these divisions are artificial, but they serve to show the extent of the damage in this disease. There is no good evidence that the disease has changed much in the last 80 years. Differences of mortality are explicable on many grounds: age, nutrition, residual immunity, underlying disease, variations in the virulence of the spirochaete due to rapid passage in an epidemic, and the availability, nature, and timing of treatment.

Disordered Physiology

We have had the opportunity to observe our patients closely; at least one of us was at the bedside continuously until the crisis had been safely passed. Although most of the observed abnormalities were probably interdependent, each system will be considered separately.

Methods

The clinical measurement of arterial and central venous pressures and the techniques of blood sampling have been described before (Parry, Bryceson, and Leithead, 1967; Schofield, Talbot, Bryceson, and Parry, 1968). The methods and calculations used for assessment of cardiovascular and pulmonary function are also described elsewhere (Warrell, Pope, Parry, Perine, and Bryceson, 1969). The measurements included oral, rectal, and skin temperatures, pulmonary ventilation, metabolic rate, blood gases, pulmonary gas exchange, acid-base balance and lactate and pyruvate concentrations, pulmonary and systemic arterial pressures, and cardiac output.

Conventional methods were employed in routine haematological investigations, urine analysis, and serum electrolyte determinations. Spirochaete densities were calculated by the standard method used in malariology, i.e. by counting the number of spirochaetes per 50 white blood cells and multiplying this total by the white blood-cell count. The more specialized methods used to

assess blood coagulation including the prothrombin times, partial thromboplastin times, fibrinogen concentration, direct platelet counts, bleeding and clotting times are described elsewhere (Perine, Parry, Bryceson, and Warrell, 1969). Other tests and methods used were as follows: erythrocyte sedimentation rate (Westergren), serum transaminases (Wroblewski and La Due, 1956), bilirubin (Malloy and Evelyn, 1937), alkaline phosphatase (Bessey, Lowry, and Brock, 1946), blood-urea nitrogen (Urograph), serum proteins (Weichselbaum, 1946), and serum protein electrophoresis (Grunbaum, Zec, and Durrum, 1963). Sternal bone marrow aspiration was performed in four patients and post-mortem examination in two others.

TABLE VII

Hepatic Function in Louse-borne Relapsing Fever

Investigation (normal value)	*No. of cases studied*	*Mean value (range)*	*No. of cases abnormal*
Prothrombin time (70–110% control)	17	60·5% (21–87%)	9
SGOT* (8–40 units/ml)	33	169 u/ml (4–1050)	20
SGPT† (0–30 units/ml)	10	43 u/ml (18–65)	8
Bilirubin (Total 0·5–1·5 mg %)	37	T = 7·0 mg % (0·3–38·4)	22
(Direct 0·2–0·8 mg %)		D = 3·2 mg % (0·1–18·2)	19
Alkaline phosphatase‡ (0·8–2·3 units/ml)	28	3·0 (0·8–9·7)	14
Serum proteins			
Total protein (7·0–8·6 g %)	28	6·6 (4·2–11·2)	17 (low)
Albumin (3·3–4·1 g %)	28	2·45 (1·62–4·37)	22 (low)
Alpha 1 (0·4–0·6 g %)	28	0·56 (0·18–0·81)	No consistent high/low pattern
Alpha 2 (0·8–1·0 g %)	28	1·02 (0·59–1·86)	
Beta (0·6–1·0 g %)	28	0·71 (0·42–1·07)	
Gamma (1·6–2·2 g %)	28	1·87 (1·18–3·20)	

* Serum glutamic oxaloacetic transaminase.
† Serum glutamic pyruvic transaminase.
‡ Expressed in International units.

Results

Hepatic function

The evidence of hepatocellular damage, which was found in almost all patients, is shown in Table VII.

The urine contained an excess of urobilinogen, and bilirubin was present in patients with jaundice. The raised serum bilirubin was accounted for mainly by the unconjugated fraction. In all the jaundiced patients the serum glutamic oxaloacetic transaminase (SGOT) was elevated; in eight of them the serum glutamic pyruvic transaminase (SGPT) was raised. The alkaline phosphatase was raised only slightly, even in those patients who had severe jaundice.

Following treatment the bilirubin fell rapidly to normal, in most cases during the first week; a persistently high bilirubin was an ominous sign (see Appendix, *Case 1*). The SGOT and SGPT also fell quickly, but in three of the 10 patients followed serially, the SGOT was still abnormally high at the end of the first week, as was the alkaline phosphatase in three of the four patients followed.

The prothrombin time was prolonged in over half the patients studied: these were not selected on account of bleeding or jaundice. Grossly abnormal values were found in some patients, particularly those with severe jaundice. The total serum protein was within normal limits in one-third of the patients studied but serum protein electrophoresis revealed a reversed A/G ratio which was associated more often with reduced albumen than a raised gamma globulin.

TABLE VIII

Renal Function in Louse-borne Relapsing Fever

Investigation (normal value)	*No. of cases studied*	*Mean value (range)*	*No. of cases abnormal*
Urine	14		
Protein			6
Erythrocytes			7
Leucocytes			9
Casts			1
Blood			
Blood urea nitrogen (8–20 mg %)	28	53 (15–260)	23
Serum Na. (135–147 mEq/l)	24	137 (130–151)	8 } No consistent high/low pattern
Serum K. (3·5–5·5 mEq/l)	24	4·1 (2·9–6·1)	7 }
Serum Cl. (100–110 mEq/l)	24	104 (86–111)	11 (low)

Renal function

The evidence for renal damage and impaired renal function is less convincing than that for hepatic damage, and our investigations are incomplete (Table VIII). Proteinuria was detected often, but it was slight and transient. Microscopic haematuria with red-cell casts, and pyuria were found in a few patients. The blood-urea nitrogen (BUN) was abnormally high in 23 out of 28 patients, but in only two of the 14 patients followed for more than five days did it remain abnormal. There was no gross or consistent abnormality of serum electrolytes.

Blood: routine investigations

The results are shown in Table IX.

In 41 out of 44 patients the haemoglobin was below 14·5 g per cent. (At the altitude of Addis Ababa the normal range is 14·5 to 18·0 g per cent.) In most patients this anaemia was normocytic and normochromic. Hypochromia was not seen. Of 22 patients followed for one week, the haemoglobin had fallen by about 1 g on the second or third day but had risen again by the seventh day.

We cannot say to what extent this could have been explained by the loss of blood through investigative procedures. The reticulocyte count was initially normal in all but one patient; three out of six followed for one week developed counts of 1·2 to 2·6 per cent. In two of these the haemoglobin had fallen slightly.

TABLE IX

Haematological Results in Louse-borne Relapsing Fever

Investigation (normal value)	*No. cases studied*	*Mean value (range)*	*No. cases abnormal*
Haemoglobin (14·5–18 g %)	44	12·0 (8·5–15·2)	41
Reticulocytes (< 1·0 %)	23	0·35 (0–1·5 %)	1
WBC/mm³ (5000–10 000/mm³)	44	8230 (2900–24 400)	14 (high)
Erythrocyte sedimentation rate (0–15 mm/hr)	27	65 (8–107)	24

The bone marrow was examined in four patients before treatment: the morphology of the red cell, white cell, and platelet precursors was normal, but there was an increase in nucleated red cells, resulting in a decreased myeloid–erythroid ratio. Spirochaetes were abundant.

The white-cell count was within normal limits in 30 out of 44 patients. In the other 14 there was a leucocytosis. In all, the count became normal within six days. The raised leucocyte count had no diagnostic or prognostic significance. The erythrocyte sedimentation rate (ESR) was raised in 24 of 27 patients. Rates above 80 mm/hr were common and correlated well with the high levels of plasma fibrinogen.

Coagulation

Epistaxis, haematuria, and purpura were seen in a quarter of the cases. The results of blood-coagulation studies are shown in Table X.

The prothrombin time was abnormally prolonged in half the patients studied; so was the partial thromboplastin time (a measure of factor VIII and IX activity). The whole-blood clotting time was *more rapid* than normal in the six patients tested, including two with prolonged prothrombin and partial thromboplastin times.

Plasma fibrinogen concentrations were significantly elevated in 12 out of 26 patients, but one patient who collapsed and died seven hours after treatment had levels consistently below 100 mg per cent; he also had thrombocytopenia and prolonged thrombin and partial thromboplastin times.

Direct platelet counts were performed in 37 patients and all but three were found to have counts below 200 000/mm³. The bleeding time was measured in 10 patients and in only one case was it prolonged. In patients with deep jaundice and other evidence of severe hepato-cellular damage, prolonged bleeding

and/or recurrent bleeding from venepuncture sites (some of which were more than 24 hours old) was occasionally noted. These patients had prolonged prothrombin and partial thromboplastin times.

TABLE X

Results of Blood-coagulation Studies in Louse-borne Relapsing Fever

Investigation (normal value)	*No. cases studied*	*Mean value (range)*	*No. cases abnormal*
Platelets ($200–400 \times 10^3/mm^3$)	37	136 000 (41 000–295 000)	34
Fibrinogen (150–400 mg %)	26	428 (90–700)	12 > 400 5 < 150
Prothrombin time (70–110% control)	17	61 (21–87)	9
Partial thromboplastin time (30–50 sec)	16	53 (35–78)	8
Bleeding time (Ivy) (2–4 min)	10	2·6 (2–5)	1
Clotting time (Lee and White) (6–10 min)	6	3·1 (1·5–4·5)	6 (decreased)

The platelet count returned rapidly to normal in most patients, usually by the third day after treatment. In only one out of 11 was it still abnormal at five days. Similarly, the prothrombin and partial thromboplastin times rapidly became normal following treatment, in parallel with the course of the SGOT and bilirubin values. The plasma fibrinogen concentrations tended to remain elevated throughout the period of convalescence; 11 out of 12 patients still had values above 500 mg per cent on the fifth day.

Spirochaete densities

Spirochaete densities calculated in a representative group of patients are shown in Table XI. There appears to be no correlation between the spirochaete density and the haemoglobin level, the platelet count or the duration of illness. Similarly, it was impossible to predict the patients' spirochaete density on the basis of his symptoms or clinical signs. A correlation probably exists between the intensity of infection and hepato-cellular injury, as shown by the consistently elevated SGOT values in the highest group. The one patient who had a spirochaete density of over 500 000/mm^3 of blood was the patient who died seven hours following treatment and is described later (see Appendix, *Case 2*).

The calculation of spirochaete densities is very crude. The procedure is not only laborious, but is also subject to wide variation depending upon the area of the blood film selected. The tendency for *Borrelia* spirochaetes to clump together just before they disappear from the blood (Schofield, Talbot, Bryceson, and Parry, 1968) makes this measurement particularly unreliable in patients undergoing a reaction.

TABLE XI

Spirochaete Densities as a Measure of the Severity of Illness in Louse-borne Relapsing Fever

Spirochaetes/mm³ blood	*No. of patients*	*Mean haemoglobin g % (range)*	*Mean SGOT units/ml (range)*	*Platelets/mm³ × 10³ (range)*	*Mean duration of illness (range)*
Under 10 000	6	12·5	42 (2–120)	130·6 (86–228)	5·3 days (3–8)
10 000–100 000	10	13·0 (12·0–13·0)	18 (9–62)	85·2 (41-130)	5·3 days (3–8)
Over 100 000	4	12·7 (12·2–13·6)	347 (78–800)	111 (41-185)	5 days (4–6)

Cardiovascular and pulmonary function

Clinical observations and electrocardiographs (ECG) were obtained in 50 patients, and detailed physiological measurements were made in 19 of these.

In 17 of the 50 patients a gallop sound was heard at some time on the day of admission. In two patients, one of whom had a loud third heart sound, there was radiographical evidence of pulmonary oedema.

The ECG findings are described in detail elsewhere (Parry, Warrell, Perine, Vucotich, and Bryceson, 1969). Multiple ventricular ectopic beats were recorded in four patients all of whom had a prolonged QTc interval which was the commonest disorder of conduction and was seen in 19 patients. Five of the 19 patients with prolonged QTc also had a prolonged PR interval. The abnormal QTc interval did not persist after the seventh day in any patient. In two of the patients who died, and in a woman with severe pulmonary oedema, the QTc interval was greatly prolonged.

All the patients were febrile on admission. Rectal temperatures ranged from 39·6 to 40·9 °C (mean 40·4 °C), but skin temperatures were relatively low.

The 19 patients studied in detail had normal chest radiographs. Tests of ventilatory capacity (forced expired volume in the first second, vital capacity, and peak expiratory flow rate) were normal in most cases; a few showed evidence of a mild restrictive defect. High oxygen intake (mean 500 ml/min STPD[1]) indicated the increased metabolic rate of these patients. Total expired ventilation was high (mean 13·5 l/min BTPS[2]), and respiratory frequency exceeded 60 breaths/min in some cases. Arterial carbon dioxide tension was low in all cases (mean 30·5 mmHg) but arterial pH was variable (range 7·30 to 7·43). Reduced arterial oxygen saturation (mean 85 per cent) resulted from a marked degree of pulmonary venous admixture which exceeded 20 per cent of the cardiac output in some cases. Arterial lactate (mean 0·7 mmol/l), pyruvate (mean 0·06 mmol/l), and glucose (mean 110 mg/100 ml) concentrations were all normal at this stage.

Cardiac output (mean 11 l/min) and heart rate (mean 120 beats/min) were increased in all cases. Brachial artery mean pressure was low (mean 77 mmHg), indicating reduced systemic vascular resistance, but pulmonary artery mean pressure was normal in the five patients in whom it was measured.

Cerebrospinal fluid (CSF)

CSF was examined in only four of our patients. The white-cell count was 3 to 84/cu mm; polymorphs and lymphocytes were present in equal numbers. No spirochaetes were seen on dark-field examination. The protein concentration ranged from 15 to 48 mg/100 ml and the glucose from 62 to 85 mg/100 ml. These results agree with those reported by Chung (1938) who examined the CSF of 26 patients with louse-borne relapsing fever. Inoculation of squirrels with CSF produced the infection although no spirochaetes could be seen on

[1] STPD = 0 °C 760 mmHg dry.
[2] BTPS = body temperature, ambient pressure, saturated.

dark-field examination. Lodewyckx (1938) observed spirochaetes in the CSF of three out of 27 cases of tick-borne relapsing fever.

Discussion

Many of the symptoms of louse-borne relapsing fever are those of hepatitis: anorexia, nausea, vomiting, and jaundice. It is not surprising, therefore, to find laboratory evidence for extensive hepatocellular damage. The urine contains an excess of urobilinogen and bilirubin if there is jaundice (Robertson, 1932; Chung and Chang, 1939). The indirect, unconjugated fraction is the main component of the bilirubinaemia (Table VII) which, together with a modestly raised alkaline phosphatase, excludes intrahepatic obstruction as the cause of jaundice. The raised transminase levels confirm that there is hepatocellular necrosis. The prolonged prothrombin time, also noted by Robinson (1942), and partial thromboplastin times are evidence that one or more of the blood-coagulation factors is deficient; this is probably due in part to the inability of the damaged liver cell to synthesize these factors (Ratnoff, 1963).

The low serum albumen is as likely to be due to malnutrition as to impaired synthesis; the irregularly raised globulins may result both from the acute infection and from past infections. Plasma fibrinogen levels are significantly elevated despite hepatocellular damage; this may reflect the response to earlier stimuli such as infection and hyperpyrexia (Ham and Curtis, 1938). The rapid clotting times observed may be due to the high concentration of fibrinogen.

Thrombocytopenia develops early in all cases. This might result either from damage to the vascular endothelium caused by the spirochaete or from sequestration in the congested, enlarged spleen (Ratnoff, 1963). *Borrelia* tend to stick to each other, and to glass, a property known as 'adhesion' (Mooser, 1958). This property, which is inhibited by immune serum, might provide a clue to the petechial rash which commonly develops early, before there is much liver damage (El Ramly, 1946): clumps of live adherent spirochaetes become impacted in capillaries and enmesh red cells, causing rupture of the capillaries, bleeding, and an increased demand for platelets. The absence of the petechial rash in relapse could be explained by action of antibody which is not strain-specific (*vide infra*: Immunological Response). Capillaries stuffed full of red cells are a histological feature of the disease before the crisis (Báez and Villasana, 1945; Levaditi, Balonet, Juminer, and Corcos, 1966). Patients with purpura or prolonged epistaxis were deeply jaundiced. Kerrest, Gambier, and Bouron (1922) and Wolff (1946) have also noted the association between severe haemorrhage and deep jaundice. No correlation could be established between the degree of thrombocytopenia and the severity of the hepatocellular damage or bleeding. Similar findings, in children, were reported by Chu, Dietrick, and Chung (1931). The finding of prolonged prothrombin and partial thrombo-plastin times, hypofibrinogenaemia and thrombocytopenia in a patient who collapsed and died raises the possibility of disseminated intravascular coagula-tion. This is considered in more detail elsewhere (Perine, Parry, Bryceson, and Warrell, 1969).

Anaemia is often present in patients with relapsing fever (e.g. Bruns, 1937; Chung and Chang, 1939). It is normocytic and normo- or hypochromic. Robertson (1932) considered it to be nutritional but Chung and Chang (1939) noticed that in a few patients it developed in the relapses, and so they considered that it could be due to the disease. The fall in haemoglobin concentration in the two days following treatment raises the possibility of haemolysis, especially during the crisis following treatment. Repeated microhaematocrit readings in five of our patients throughout the crisis varied by no more than three per cent. Nevertheless, Banwell and Kibukamusoke (1963) found evidence of haemolysis which was severe enough to cause jaundice in a patient with tick-borne relapsing fever. Also in experimental animals infected with *B. recurrentis* there is an anaemia (Sparrow, 1958) which presents acutely at the crisis (Calabi, 1959) and which is followed by a reticulocytosis (Robertson, 1935). Although only three out of seven patients with 1 g drop in haemoglobin following treatment developed a slight reticulocytosis (1·2 per cent–2·6 per cent), we believe that there may sometimes be a mild degree of haemolysis in louse-borne relapsing fever which may happen, or become more marked, at the time of the crisis. Bone-marrow studies support this (Sabalette, Dominguez, and Iglesias, 1947; Anderson and Zimmerman, 1955).

The raised blood-urea nitrogen, also noted by Benhamou (1945), is probably due to renal damage, but may in part be due to dehydration or to a failure of deamination, which is implied by the observation of Godel (1946) of an increased urinary excretion of non-urea nitrogen. Our findings of transient proteinuria, haematuria and red-cell casts in four patients are consistent with those of Carter (1882), Feroluzzi (quoted by Bucco, 1965) and Chung and Chang (1939) who attributed these findings to a transient, acute nephritis. We have no other evidence for acute nephritis in our patients: the urinary findings could have resulted from pyrexia, dehydration, and micro-haemorrhages in the renal medulla.

There was considerable evidence, both clinical and electrocardiographic, of abnormal myocardial function in about half of our patients. The defects of conduction are generally recognized as evidence of myocarditis. In most of the patients with gallop rhythm the added sound was atrial and probably resulted from the high output state, but in some there was evidence of cardiac failure (*vide infra*: The Reaction to Treatment).

Immunological Response

We have no experimental observations of our own to add to the extensive literature on the subject. The evidence is, however, piecemeal and scattered over 60 years. Results of investigations have often been contradictory. Meleney (1928), Schuhardt (1942), and Felsenfeld (1965) have critically reviewed the data and the methods of investigation used, but there has never been any attempt to put the pieces together and to build up a picture of how and in what sequence the patients' defence mechanisms respond to a borrelial infection. We try here to do this.

THE MORBID ANATOMY

Three of our patients died: in two of them autopsy was performed. The case histories and post-mortem findings are given as an Appendix. In the first case death was probably due to liver failure, but the presence of regenerating nodules in the liver suggested a pre-existing hepatitis. The multiple sterile infarots in the spleen were considered by Russell (1931) to be characteristic of relapsing fever. The widespread small haemorrhages found in both our cases were also noted by El Ramly (1946*b*) who described the post-mortem findings in 122 patients who died with internal bleeding. In the second case no single cause of death could be found but disseminated intravascular coagulation, myocarditis, and cerebral oedema probably contributed. Judge, Samuel, Vukotich, and Perine (1969) describe the typical myocardial damage seen in patients who died shortly after the crisis.

We shall not describe in detail the post-mortem appearances of louse-borne relapsing fever as good accounts are available elsewhere (Belezky and Umanskaja, 1930; Russell, 1932, 1933; Báez and Villasana, 1945; Anderson and Zimmerman, 1955; and Levaditi, Balouet, Juminer, and Corcos, 1966). These reports make two things clear: first, that some early reports (e.g. Kulescha and Titowa, 1923) have not distinguished between the pathology of relapsing fever and of complicating bacterial infections, and secondly, that the pathology of the disease and the pathology of the crisis are two different things.

THE PROGNOSIS

We can only draw cautious conclusions from our studies as we treated only 62 patients. Of these three died—a mortality of 5 per cent, no better than the 4 per cent reported by the Italians (Bucco, 1965). We have previously mentioned the ominous signs of shock and coma. These complications were seen in patients who presented themselves for treatment late in the course of their infection with heavy spirochaetaemia. All who have written about the disease are agreed that deep jaundice, coma, and shock are grave prognostic signs. Several people commented that early treatment improved the prognosis, but Wolff (1946) was quite adamant that it was dangerous to treat a patient who was approaching the end of his attack: the reaction after treatment in a heavily infected patient with a high fever is worse than the spontaneous one. We agree with Wolff about the severity of this crisis, but have not had the courage to withhold treatment.

Most of our patients recovered dramatically from the symptoms of their infection; but remained exhausted for the next day or two. Myocardial damage, as shown particularly by a prolonged QTc interval, can persist for several days following treatment and may cause an unexpected death.

In an outbreak of relapsing fever, intercurrent illness can make the prognosis much worse, particularly Salmonella infections (Kulescha and Titowa, 1923; Ingraham and Lapenta, 1946; Anderson and Zimmerman, 1955), and typhus which was rampant in the 1919–20 epidemic (Willcox, 1920). Louse-borne

relapsing fever has been reported to unmask latent malaria and kala-azar (Corkhill, 1948).

The different mortality rates in epidemics have already been discussed in relation to the increased virulence of the organism and to the nutritional state of the patient.

The causes of death in louse-borne relapsing fever can now be summarized, their pathology having been already discussed.

The disease:	early:	none
	late:	haemorrhage due to prothrombin deficiency
		hepatic coma
		myocarditis
		disseminated intravascular coagulation
The crisis:	early:	hyperperexia with convulsions
	late:	myocardial failure
		'shock'
		cerebral oedema

SUMMARY

Louse-borne relapsing fever is still capable of causing another pandemic. We have reviewed the epidemic history of the disease and considered the past and present importance of the endemic focus in Ethiopia. The characteristics of the organism, its vector and its host—man—that are most relevant to an understanding of the pathology and epidemicity of the disease have been discussed.

We have studied 62 patients with louse-borne relapsing fever in Addis Ababa, Ethiopia, from 1966 to 1968. The clinical presentation varied. Fever, headache, skeletal and abdominal pain, and the usual symptoms of acute infection were common. Tachypnoea and upper abdominal tenderness with a palpable liver and spleen were found in two-thirds of the patients, jaundice in one-third, and purpura in one-sixth.

Thrombocytopenia was the rule. Biochemical evidence of hepatocellular damage was found in most patients. Myocardial damage was suspected in one third of them. Pulmonary ventilation and cardiac output were increased and there was evidence of impaired gas exchange. Evidence of renal and cerebral damage was less striking.

The literature on the immune response has been reviewed in order to understand the phenomenon of the crisis. Treatment was with intravenous tetracycline, and was followed by a Jarisch-Herxheimer reaction. We have described in detail the clinical and physiological features of this reaction. Spirochaete death and phagocytosis, resulting in the release of endogenous pyrogen, may be responsible for all its features. Hyperpyrexia in the chill phase and hypotension and cardiac failure in the flush phase can be fatal, and we suggest how these complications should be managed.

The difficulties in interpreting the morbid anatomy are illustrated by two cases. The mortality was 5 per cent. We have emphasized the epidemic and pathological processes which determine the prognosis.

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APPENDIX

Case Histories and Post-mortem Findings of Two Patients who Died of Louse-borne Relapsing Fever

Case 1. A 14-year-old Gurage boy had had headache, fever, and dizziness for three days. He was comatose on admission with a very stiff neck, deep jaundice, widespread purpura, and an enlarged liver and spleen. A blood slide showed spirochaetes, density 30 000/mm^3. Pertinent laboratory findings were: total bilirubin 6·0 mg per cent (direct 2·7 mg per cent), SGOT 57 units/ml, alkaline phosphatase of 3·2 units/ml, haemoglobin 10 g per cent, and normal cerebrospinal fluid. He was treated with 150 mg tetracycline intravenously and a typical reaction ensued. He remained comatose following treatment; convulsions occurred on the second day following treatment and persisted until death two days later. At autopsy the brain was oedematous, and the liver enlarged and distorted by nodular regeneration. The spleen was enlarged and congested with multiple macroscopic infarcts. Small haemorrhages were found in the serosal surfaces of the gut, in the endocardium, the visceral and parietal pleura, the renal capsule, and the pia mater.

Case 2. A 23-year-old Amhara man gave a history of fever, malaise, anorexia, and abdominal pain for six days. He was able to walk into the hospital. Examination revealed deep jaundice, a petechial rash over the trunk, and a moderately enlarged and tender liver and spleen. The haemoglobin was 11·2 g per cent, BUN 60 mg per cent SGOT, 420 units/ml, alkaline phosphatase

9·7 units/ml, prothrombin time 10 per cent normal control, partial thromboplastin time 67 sec, and fibrinogen 90 mg per cent. The platelet count was 185 000/mm³ and the spirochaete density 500 000/mm³. He was treated with 250 mg tetracycline intravenously. After the reaction he became restless and confused. Two hours later he appeared to be resting comfortably, but his level of consciousness was declining. Seven hours after treatment he collapsed and died. At autopsy the brain was moderately oedematous, the liver enlarged, and the spleen normal. The heart was grossly normal. Diffuse, micro-haemorrhages were found in all serosal membranes, the renal medulla, and lungs.

Microscopic examination of the tissues from both cases showed small blood-vessels congested with blood. The spleen from *Case 1* showed numerous small, sterile infarcts and the liver showed multiple regenerating nodules of varying size. Microscopic haemorrhage was found in the myocardium, kidneys, and lungs of *Case 2*. Death was attributed to hepatic failure in *Case 1*, the liver being compromised by a pre-existing hepatitis. No cause of death could be definitely established in *Case 2*, but disseminated intravascular coagulation, myocarditis, and cerebral oedema could all have contributed.

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It is assumed that immunity develops in man after an attack of relapsing fever that has resolved spontaneously, as reinfection during an epidemic is rare (Omar, 1946). Immunity has been shown to be specific to the strain of spirochaete causing the relapse (Russell, 1933; Cunningham, Theodore, and Fraser, 1934; Felsenfeld, Decker, Wohlhieter, and Rafyi, 1965). In an attack of louse-borne relapsing fever there are usually only one or two, and never more than four relapses, while there are at least nine strains of *B. recurrentis*, which are antigenically distinguishable (Cunningham, Theodore, and Fraser, 1934), so it is possible to understand the occasional reinfection (Meleney, 1928). The duration of immunity in man is not known. It lasts at least 10 months (Ballif, Constantinesco, and Chelaresco, 1947). Stein (1944) has demonstrated a low titre of antibodies in a patient 36 years after his illness. Immunity is probably sterile (Russell, 1933).

Despite the inherent periodicity of *Borrelia*, it is likely that each attack is terminated by the action of serological antibodies (*vide supra*: The Organism). Immunization starts at the time of inoculation or at the start of each remission and not with the overt infection, and there is time for antibodies to develop even though the phase of spirochaetaemia may be only one day in the later relapses. The presence of these antibodies has been repeatedly demonstrated (Meleney, 1928; Russell, 1933; Cunningham, Theodore, and Fraser, 1934; Coffey and Eveland, 1967). They make their appearance shortly before the crisis (Calabi, 1959) and reach a peak just after the crisis (Ballif, Constantinesco, and Chelaresco, 1947). These antibodies are protective (Robertson, 1932; Calabi, 1959) and curative. Immune serum injected intravenously into a patient causes a typical crisis in 10 to 30 minutes (Balteanu, Russ, and Voiculescu, 1948), although not all workers (Adler and Ashbel, 1937) have been able to show this. The efficacy of these antibodies contrasts sharply with the inefficacy of phagocytosis: that is phagocytosis of live organisms before the crisis (Kritschewski and Sinjuschina, 1931; Belezky and Umanskaja, 1930).

The action of these antibodies has been extensively studied *in vitro*. They cause agglutination and immobilization and lysis of the spirochaete (Meleney, 1928; Cunningham, Theodore, and Fraser, 1934; see also Felsenfeld, 1965). These two actions can be separated (Robertson, 1932; Adler and Ashbel, 1937); lysis is complement dependent (Felsenfeld, Decker, Wohlhieter, and Rafyi, 1965). Adler and Ashbel (1937) have described a third action of immune serum, which caused spirochaetes to attach themselves to white cells of all classes and to bore into their cytoplasm. This activity could be called leucotactic. Phagocytosis was followed by vacuolation of the cytoplasm, a phenomenon that has been observed late in severe infections (Robertson, 1932) and at the crisis (Schofield, Talbot, Bryceson, and Parry, 1968).

Calabi (1959) showed that antibodies were present in both the β and γ globulin fractions. Felsenfeld, Decker, Wohlhieter, and Rafyi (1965) have looked closely at the chemical and antigenic structure of *B. parkeri* and *B. turicatae*. They found one common and three species specific groups of antigens which they called A, B, and C. A and C conferred specificity on the relapse strains, and gave

rise to agglutination and lytic antibodies which were detected in the β and γ globulin fractions. Felsenfeld and Wolf (1969) later showed that, in monkeys infected with *B. turicatae*, the waves of strain specific antibodies that followed each spirochaetemia corresponded with large waves of IgM and small rises of IgG. The prolonged high titres of antibody that persisted after the infection were, however, associated with raised levels of high-affinity IgG, which seems to take over from the more evanescent low-affinity IgM. They also examined the sites and function of immunologically active cells in lymph-nodes taken during the course of the infection. Immunologically *Borrelia* behave like trypanosomes.

TREATMENT

Results

In all but three cases we gave tetracycline—the evidence for the value of this antibiotic is discussed below. We abandoned the use of tablets early in our studies because two patients vomited after an oral dose of 250 mg tetracycline. 250 mg by intravenous injection over two to three minutes was adopted as standard initial treatment. The blood was cleared of spirochaetes within 2½ hours. In all patients treatment was followed by a characteristic reaction (*vide infra*: The Reaction to Treatment). 50 mg provoked no reaction, and had no effect at all on the number of spirochaetes in blood films. 150 mg by intramuscular injection proved effective in clearing the peripheral blood of spirochaetes if two doses separated by an interval of six hours were given.

Two patients, the second of whom was a pregnant mother at full term in whom a vigorous reaction might have endangered the foetus, were given as initial treatment penicillin 80 000 units (20 000 crystaline and 60 000 procaine) by intramuscular injection every six hours. The blood of the first was cleared of spirochaetes after the fifth injection. Her temperature only rose from 40·7 °C to 41·2 °C three hours after the first 80 000 units. (The mean rise in the patients who received tetracycline was 1·6 °C, range 1·0 to 2·2 °C). It then fell slowly to 37·5 °C at the time when spirochaetes disappeared, 29½ hours after the first injection of penicillin. The pregnant mother was not studied in detail; she had a trivial reaction and was delivered of a normal full-term infant.

One patient underwent a spontaneous reaction, with clearance of spirochaetemia (Schofield, Talbot, Bryceson, and Parry, 1968).

We have no certain evidence about the total dose of tetracycline necessary for treatment; we have seen no relapse in 45 patients after a total dose of 4·5 to 5·5 gm given over four to five days, nor in 18 patients who received only 250 mg. One patient became reinfected three weeks later. In addition to the antibiotic, vitamin K 20 mg was given intramuscularly. The management of the reaction is considered separately.

Discussion

Neo-arsphenamine was widely used until the antibiotics were discovered. It was valuable particularly during epidemics (Garnham, Davies, Heisch, and

Timms, 1947) when it reduced mortality dramatically: from 40 per cent to 4 per cent in the Kenya epidemic. The use of antibiotics was reviewed by Schuhardt (1952). Penicillin was used by Taft and Pike (1945) who commented on its efficacy and on the reaction which it caused. *B. recurrentis* is killed in two hours by penicillin at a concentration of 10 units/ml, and in six to eight hours at 0·62 units/ml. Sénécal and Ahmad (1950) claimed that the louse-borne spirochaete of Afghanistan was resistant because the blood was not always rapidly cleared of spirochaetes; but all their patients showed a fall of temperature. This slow clearance does not necessarily mean that the drug has failed. Penicillin is poor at clearing the residual infection in the brain, even in very high doses, and this makes it unsuitable for use in the treatment of the tick-borne disease especially as several strains of tick-borne spirochaete are insensitive to penicillin. The problem of residual brain infection and relapse in the louse-borne disease exists, as can be seen from the arsenical days (Wolman, 1944). Ingraham and Lapenta (1946) showed that penicillin reduced the relapse rate from 87 per cent to zero, but Harrison and Whittington (1951) and Rÿkels (1968) both encountered relapse after treatment with penicillin; they also noticed prolonged spirochaetaemias.

Tetracycline, *in vitro*, at a concentration of 5 μg/ml, kills spirochaetes in two hours; this is equivalent to an adult human dose of 125 mg. It has the advantage that it clears the brain of infection and reduces the relapse rate in tick-borne relapsing fever although the dose may have to be high. Sampedro and Andrey (1956), treating patients suffering from *B. hispanica* needed to give 250 mg tetracycline three hourly, to a total dose of 6 to 8 g or 2 g weekly for three to four weeks in order to reduce the relapse rate to 3 per cent from the 40 per cent which followed the single 2 g course. Apart from Rÿkels's (1968) and our data, little is known of its use in louse-borne relapsing fever. Chloramphenicol is effective in curing patients of louse-borne relapsing fever after a total dose of 1 g (Hirschboeck, 1954); there have been no studies of its efficacy in preventing relapses. Streptomycin has been successfully used in mice (Heilman, 1945).

The prevention of relapse must be one of the aims of treatment. It is clear that a relapse of louse-borne relapsing fever can sometimes follow treatment with penicillin. Rÿkels (1968) followed up his penicillin group who were treated with 400 000 units of procaine penicillin initially and then with 800 000 units daily for three more days, and his tetracycline group who were treated with 250 mg initially, followed by a single dose of 500 mg. His follow-up studies, however, were incomplete; only 35 of his 67 patients came back and so his results cannot be taken definitively, but he noted that there were two relapses in his penicillin group and none in his tetracycline group. Neither could we follow up our patients adequately and, apart from one who was probably reinfected, we are unaware of any relapse following a single 250 mg dose of tetracycline.

The treatment of louse-borne relapsing fever in an epidemic must take into account the efficiency and the cost of the drugs. It is probable that the safest, most effective, and economical method of treating louse-borne relapsing fever

would be one injection of 300 000 units of procaine penicillin followed the next day by an oral dose of 250 mg tetracycline. The preference for the initial use of penicillin over tetracycline is discussed below (Management of the Crisis). Chloramphenicol might be just as good and even cheaper. In a pandemic, treatment with a cheap long-acting penicillin, e.g. penicillin aluminium monostearate, should replace arsenicals as the adjunct to widespread use of D.D.T.

THE REACTION TO TREATMENT

Clinical Features

The reaction which followed treatment with tetracycline has been described before (Parry, Bryceson, and Leithead, 1967; Schofield, Talbot, Bryceson, and Parry, 1968). The clinical pattern was characteristic. All patients had a vigorous rigor. Just before its onset they became uncomfortable, restless, and anxious. Some had a sudden urge to pass urine, or to vomit. The rigors began 40 to 105 (mean 60) minutes after tetracycline injection and lasted 10 to 30 minutes. Rectal (and skin) temperatures rose briskly to 40·0–41·8 °C (mean 41·5 °C), but the patients felt cold. Their foreheads were hot but the hands remained cold. There was no sweating. Respiratory and pulse-rates, and blood-pressure rose strikingly. Respiration was interrupted by the intense shivering. This phase of the reaction was most distressing for the patients who often wailed in fear and misery. Two of our patients became disorientated; delirium, coma, vomiting, diarrhoea, paroxysmal cough, and limb pains were occasionally observed. After the rigor had ended the patients suddenly felt hot. The rectal temperature rose to its peak of 41·1 to 42·6 °C (mean 42·0 °C) 75 to 190 minutes (mean 125 minutes) after tetracycline, 20 to 75 minutes (mean 45 minutes) after the start of rigors. Skin temperatures also rose to a peak at about the same time and then fluctuated wildly. About the time that the temperature reached its peak spirochaetes disappeared from the peripheral blood.

Arterial pressure fell at the beginning of this flush phase, a profuse sweat broke out, and later the hands became warm. The patients then felt progressively more comfortable and asked for food and drink. By the end of the day they were exhausted and fell asleep. The temperature fell slowly; after eight hours it was still between 37·7 and 40·3 °C (mean 39·3 °C) but by morning it was normal in all cases.

This reaction has the characteristics of the Jarisch-Herxheimer reaction (Schofield, Talbot, Bryceson, and Parry, 1968).

Physiological Changes

Four phases were recognizable during the reaction to treatment (Warrell, Pope, Parry, Perine, and Bryceson, 1969). A *prodromal phase* after tetracycline injection was uneventful, until shortly before the rigors began when increases in blood-pressure, pulse-rate, and cardiac output were detected.

The start of the *chill phase* was announced by the sudden onset of rigors and an abrupt rise in body temperature (mean rise 1·2 °C). Oxygen intake

increased to more than 1 l/min in some cases (mean 830 ml/min) which is equivalent to that required in moderately severe exercise. The increase in total ventilation to a mean of 29 l/min was in excess of metabolic demands as shown by the fall in arterial carbon dioxide tension to a mean value of 24 mmHg. Respiratory alkalaemia resulted. Despite the overbreathing arterial oxygen saturation decreased slightly to a mean of 83 per cent. Pulmonary venous admixture had increased to a mean of 20 per cent of cardiac output (range 10 to 40 per cent) suggesting impaired pulmonary gas exchange. Brachial artery mean pressure rose sharply at the onset of the chill phase to reach maximum values of 84 to 121 mmHg. Cardiac output rose to a mean of 15·5 l/min and heart-rate to 140 beats/min. Total systemic vascular resistance rose slightly above pre-treatment level at the very beginning of the chill but later fell. Pulmonary artery mean pressure and pulmonary vascular inflow resistance both fell at that time.

As the shivering stopped, brachial artery pressure fell suddenly and the *flush phase* began. In most patients the pressure remained below 60 mmHg for the next eight hours. The lowest point, which lay between 36 to 71 mmHg, was recorded two to nine hours after the rigors. Cardiac output remained high at a mean value of about 10 l/min which indicated that the hypotension was the result of low systemic vascular resistance. In contrast pulmonary artery mean pressure rose to 18 to 34 mmHg, indicating increased pulmonary vascular resistance. Pulmonary ventilation decreased during this phase. As the respiratory alkalosis declined a metabolic acidosis was revealed. This acidosis was only partly explained by a rise in arterial lactate concentration to a maximum of 1·0 to 1·9 mmol/l (mean 1·4 mmol/l), four hours after the rigors. In four patients who breathed 100 per cent oxygen throughout the reaction this mild lactic acidosis did not develop. A rise in arterial glucose concentration to a mean of 175 mg/100 ml was also prevented by breathing 100 per cent oxygen.

The onset of a *phase of recovery* or '*defervescence*' was usually detectable within eight hours of the rigor. By the next morning when all patients were afebrile respiratory measurements were virtually normal, but brachial artery mean pressure remained low and cardiac output was still high.

Clinical and ECG evidence of disturbed myocardial function before treatment has already been described (*vide supra*: Disordered Physiology). In some patients the abnormalities appeared or became more marked during the course of the reaction which followed treatment. The profound fall in systemic arterial pressure which was observed in 38 of the 50 patients was not considered to be due chiefly to myocardial abnormality (*vide infra*: Management of the Reaction), although this might have contributed. A rise in central venous pressure about four to six hours after the rigors was seen in six patients: this was thought to be evidence of myocardial dysfunction, particularly as a prolonged QTc interval, and a gallop rhythm were observed in these patients. To three of the six patients with elevated central venous pressures 1·0 mg of digoxin was given intravenously. The central venous pressure fell rapidly. Further evidence of a precarious myocardium was provided by the observed

effect of a rapid infusion of 600 ml of a plasma expander in a patient whose systemic arterial pressure was very low. There was a dramatic rise in venous pressure and the patient became distressed and dyspnoeic; crepitations were heard in lung fields that had been clear previously and the arterial pressure was not improved.

Some ECG abnormalities which appeared during the reaction to treatment suggested acute right heart 'strain', namely T-wave abnormalities in the right chest leads, complete or partial right bundle branch block, large secondary R-wave in lead aVR, acute right axis deviation, acute clockwise rotation, and increased right atrial P-wave voltage. Other changes at this time were multiple ventricular ectopic beats and prolonged QTc interval. None of these abnormalities persisted for more than a few days after treatment.

Discussion: Mechanism of the Reaction

The reaction starts as spirochaetes are cleared from the peripheral blood. Its severity depends upon the speed at which they disappear (*vide infra*).

We have studied, by serial estimations of spirochaete densities, the speed with which they disappeared from the peripheral blood following treatment with tetracycline (250 mg). The results, given in Table XII, show that there was no uniform pattern of disappearance. However, they usually disappeared around the time the leucocyte count was at its lowest (*vide infra*).

The mechanism by which spirochaetes are removed from the blood following treatment is imperfectly understood. In the untreated patient it is probable that antibodies, reaching sufficient titre, immobilize and start to lyse spirochaetes. Phagocytosis, aided by leucotaxis (Adler and Ashbel, 1937), can now take place and spirochaetes are filtered off by the reticuloendothelial system (Russell, 1931; Belezky and Umanskaja, 1930) especially by the spleen, where they are found in great numbers at this time (Nikiforoff, 1893, quoted by Anderson and Zimmerman, 1955; Russell, 1932), and where they may be found after they have disappeared from other organs and from the blood. Circulating leucocytes also take up spirochaetes (Schofield, Talbot, Bryceson, and Parry, 1968). Agglutinating antibodies possibly cause great clumps of spirochaetes, which can be seen on a blood slide, to impact in capillaries and cause multiple ischaemic or even haemorrhagic foci which are manifest clinically by vomiting, diarrhoea, cough, pain, aphasia, confusion, delirium, and coma: all of which signs we have observed transiently at the crisis (see also Bruns, 1937). The spleen shows minute necrotic spots (Russell, 1932*a*) and may even be infarcted (e.g. El Ramly, 1946*a*) with the later development of sterile abscesses (Nasr, 1948).

The way in which antibiotics kill spirochaetes is not known (Schuhardt, 1952) but the speed and fury of the reaction that follows their administration suggest that their ultimate action is not unlike that of antibodies. They act too fast to be simply bacteriostatic.

As the reaction starts, striking changes are seen in the circulating leucocytes

TABLE XII

Spirochaete Disappearance After Treatment

Case no.	*Start of Treatment*	*Spirochaetes per cubic millimetre of blood* +15 *min.*	+30 *min.*	+45 *min.*	+60 *min.*	+75 *min.*	+90 *min.*	+105 *min.*	+120 *min.*	+135 *min.*	+150 *min.*
1.	42 000	—	50 400*	1	0						†
2.	366 000	—	62 800*	—	2930†	—	1	—	0		
3.	2800	—	2020	—	0*		†				
4.	42 200	—	—	53 100	59 600	47 000	—	27 550*	10 400†	4920	0
5.	32 500	43 050	13 900	1280*	0	†					
6.	2620	1470	840	1220	0*		†				
7.	156 100	133 000	87 200	65 900	38 100*	32 200†	27 800	4150	150	0	
8.	37 650	19 350	6180*	2090	300†	0					
9.	246 500	258 000	254 000	8880	—	4090	3800	1910	1440*	1100	0†
10.	830	0						†*			
11.	12 380	2420	740*	740	0†						
12.	33 600	29 300	15 000	5260*	3660	0†					
13.	2080	—	1060	—	400	—	0*				†
14.	7200	—	2050*	380	0†						
15.	15 120	10 440	760	0*		†					
16.	26 180	20 750	21 920	15 200	11 520	11 520	6970	400*	0†		

* Onset of rigor. † Lowest leucocyte count.

(Schofield, Talbot, Bryceson, and Parry, 1968). Before the spirochaetes disappear, whether spontaneously or after an antibiotic, the leucocyte count falls abruptly. It is lowest when the spirochaetes disappear, about one hour after treatment, and then rises quickly to its original level. As the leucocyte count falls, so the temperature rises. Both polymorphs and lymphocytes disappear. The morphology of the polymorphs also changes. Vacuoles appear in, and granules disappear from, the cytoplasm. The fall of the polymorph count is not associated with any significant rise of the serum muramidase. This suggests that the cells are being transiently sequestered and are not being destroyed in large numbers (Perine, McCafferty, and Parry, 1969).

Phagocytosis of dead organisms results in the release of leucocyte, or endogenous, pyrogen from leucocyte granules (Berlin and Wood, 1964, Bodel and Atkins, 1966). Schofield, Talbot, Bryceson, and Parry (1968) have suggested that it is a sudden release of endogenous pyrogen that accounts for the features of the reaction both in relapsing fever and in syphilis, namely the aggravation of local lesions, the fever and the cardiorespiratory changes. We have since been able to demonstrate pyrogenic activity in the plasma of patients taken during the crisis and have shown that blood taken at this time will, when reinjected the following day, reproduce all its features (Bryceson, Cooper, Warrell, Perine, and Parry, 1969). The actions of endogenous pyrogen have been reviewed by Cranston (1959, 1966) and by Cooper (1968).

Local release of endogenous pyrogen, as may follow phagocytosis of spirochaetes in the tissues, causes local inflammation (Moses, Ebert, Graham, and Brine, 1964) which could result in an exacerbation of symptoms, such as we have observed, and signs, particularly of myocardial damage which are often striking at this time, and possibly of cerebral oedema which may have contributed to the death of one of our patients (Appendix, *Case 2*). Endogenous pyrogen released systemically reaches the hypothalamus and causes a brisk rise in temperature with, initially, vasoconstriction. Temperatures as high as 42 °C may result in cerebral oedema (*British Medical Journal*, 1968), convulsions, and death (Wolff, 1946).

The cardiorespiratory disturbances may also be the result of the sudden release of pyrogen into the circulation. Increased body temperature *per se* stimulates respiration and circulation, but the changes during the reaction to treatment were disproportional to the absolute body temperature and to its rate of rise. In two patients who received 3 to 4 g of hydrocortisone by infusion, rectal temperatures at the start of rigors were 2 °C lower than those of the control group but the changes in ventilation and circulation were no less marked. The effect of hydrocortisone in reducing the baseline temperature and its failure to prevent the rise in temperature during the reaction is interesting in view of its known stabilizing effect on lysosome membranes (Weissman, 1965). These physiological disturbances are still seen, in patients given endotoxin, even when fever is prevented by the administration of amidopyrine (Bradley, Chasis, Goldring, and Smith, 1945).

These findings and the result of the reinjection experiment described above

suggest that the observed cardiorespiratory disturbances may be the result of actions of pyrogen separate from its effect on body temperature.

Continuous '100 per cent' oxygen therapy throughout the reaction did not modify the changes in ventilation and circulation (including the late rise in pulmonary artery pressure) but the lactic acidosis was prevented suggesting that it may have resulted from some form of 'tissue hypoxia'. The effect of oxygen suggests that other known causes of lactic acidosis such as fever, respiratory alkalosis, excess catecholamine production, and spirochaetal metabolism (Fulton and Smith, 1960), were not important in these patients.

Management of the Reaction

Antibiotics. In our patients intravenous injection of 250 mg of tetracycline was successful in clearing the blood of spirochaetes within three hours, but in all cases a severe febrile reaction was produced. We were unsuccessful in finding a dose of tetracycline and a mode of administration which was therapeutically effective and yet produced less reaction. We think it unlikely that altering the dose of an antibiotic will affect the reaction, but the rate of absorption may influence its severity. We have tended to treat with divided doses of penicillin every six hours (*vide supra*: Treatment) patients in whom a marked reaction was particularly undesirable, but we have insufficient evidence to advocate this regime with confidence. Rÿkels (1968) has compared the effects of 400 000 units of intramuscular procaine penicillin and of 250 mg of oral tetracycline on the severity of the crisis. From his observations of the patients and from his measurements of the changes of temperature, blood-pressure, heart-rate, and respiratory rate, he concluded that the reaction was less severe after penicillin. He also noted that the clearance of the blood was slower after penicillin, mean eight to nine hours, than with tetracycline, mean four to five hours. Stuart (1945), who experimented with different arsenical preparations, observed that the severity of the crisis depended upon the speed of spirochaetal lysis which in turn depended upon the arsenical preparation used. Experience with syphilis (*British Medical Journal*, 1967) suggests that the Jarisch-Herxheimer reaction is an all-or-none phenomenon, and Taft and Pike (1945) noticed that whereas 20 000 units of penicillin neither killed the spirochaete nor produced a reaction, 40 000 units did both.

Hydrocortisone. We have attempted, without success, to modify the reaction by giving hydrocortisone. At first a single intravenous dose of 100 mg was given (Parry, Bryceson, and Leithead, 1967) but subsequently two patients were given continuous infusions of 20 mg/Kg body-weight/hour for four hours starting one hour before tetracycline injection. Although body temperature was depressed before the onset of rigors the reaction was subjectively and objectively no less severe than in the control group, and the fall in blood-pressure was not prevented.

Hyperpyrexia. Fatal febrile convulsions at the peak of the reaction have been

reported by Wolff (1946) and others but we have not seen this complication. Hyperpyrexia may develop rapidly. We employed energetic tepid (> 18 °C) sponging and fanning if the rectal temperature rose towards 42 °C (107·6 °F). It is unlikely that salicylates and other antipyretics would be effective in preventing the temperature rise during the reaction.

Cardiovascular. Most of the deaths following treatment which have been reported in the literature, and the three in the present series, occurred during hypotensive period several hours after the rigor. Rectal temperature was still elevated at that time and it is evident that the continuing demand for cutaneous vasodilation to dissipate heat, and the dilatation of renal and splanchnic beds by pyrogen (Bradley, Chasis, Goldring, and Smith, 1945; Bradley and Conan, 1947), imposes a low relatively fixed resistance on the systemic circulation. Under these circumstances a reasonable blood-pressure can be held only by maintaining a high cardiac output.

Two factors may be important in preventing the maintenance of cardiac output during this phase of the reaction: myocardial failure, and dehydration. Acute cardiac failure has been observed and effectively treated with parenteral digoxin in some patients (Parry, Bryceson, and Leithead, 1967): myocarditis is a frequent autopsy finding (Anderson and Zimmerman, 1955; Judge, Samuel, Vukotich, and Perine, 1969). Dehydration may result from sweating, increased respiratory-tract evaporation due to overbreathing and fever, and failure to drink. In one patient severe hypotension (50/30 mmHg) which developed 10 hours after the rigors was corrected by saline infusion.

Impaired postural control of blood-pressure during endotoxin-induced fever has been shown to allow hypotensive collapse on standing (Bradley, Chasis, Goldring, and Smith, 1945; Grimby, 1962). This may have contributed to the sudden death of one of Rÿkels's (1968) patients when he got up several hours after treatment. In most cases severe hypotension may be prevented by careful attention to fluid intake. Oral fluids may prove adequate. If the systolic pressure drops below 60 mmHg the foot of the bed should be raised. If intravenous infusion becomes necessary it should be monitored by the venous pressure for fear of myocardial damage. In patients who develop signs of acute cardiac failure rapid digitalization may prove effective. Patients should be confined to bed for at least the first 24 hours after treatment to prevent disastrous episodes of postural hypotension.

Systemic vascular resistance may be increased by adrenergic vasopressor drugs. These have been used in a few patients and occasionally produced a sustained rise in blood-pressure. There are theoretical reasons why these drugs might be effective (Thomas, Zweifach, and Benacerraf, 1957), but a disadvantage of vasoconstrictor drugs is that by decreasing skin blood flow they could interfere with heat loss.

Tissue hypoxia. The metabolic abnormalities which appeared during the period of hypotension may have resulted from tissue hypoxia. Their prevention by continuous '100 per cent' oxygen therapy should encourage the use of oxygen during the treatment of severe cases.

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13. ABSTRACT

Louse-borne relapsing fever is still capable of causing another pandemic. We have reviewed the epidemic history of the disease and considered the past and present importance of the endemic foci in Ethiopia. The characteristics of the organism, its vector and its host-man that are most relevant to an understanding of the disease have been discussed.

We have studied 62 patients with louse-borne relapsing fever in Addis Ababa, Ethiopia, from 1966 to 1968. The clinical presentation varied. Fever, headache, skeletal and abdominal pain, and the usual symptoms of acute infection were common. Tachypnoea and upper abdominal tenderness with a palpable liver and spleen were found in two-thirds of the patients, jaundice in one-third, and purpura in one-sixth.

Thrombocytopenia was the rule. Biochemical evidence of hepatocellular damage was found in most patients. Myocardial damage was suspected in one third of them. Pulmonary ventilation and cardiac output were increased and there was evidence of impaired gas exchange. Evidence of renal and cerebral damage was less striking.

The literature on the immune response has been reviewed in order to understand the phenomenon of the crisis. Treatment was with intravenous tetracycline, and was followed by a Jarisch-Herxheimer reaction. We have described in detail the clinical and physiological features of this reaction. Spirochaete death and phagocytosis, resulting in the release of endogenous pyrogen, may be responsible for all its features. Hyperpyrexia in the chill phase and hypotension and cardiac failure in the flush phase can be fatal, and we suggest how these complications should be managed.

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12. SPONSORING MILITARY ACTIVITY

ABSTRACT

The difficulties in interpreting the morbid anatomy are illustrated by two cases. The mortality was 5 per cent. We have emphasized the epidemic and pathological processes which determine the prognosis.

14 KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Relapsing Fever						
Louse-borne relapsing fever						
Borrelia						
B. Spirochaetes						
B. recurrentis						
B. parkeri						
B. turicatae						
Taxonomy						
Spirochaete densities						
Hepatic function						
Renal function						
Blood						
Cerebrospinal fluid (CSF)						
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